Formulation, Development and Production of Anticancer agent

Sample Task Order
Request/statement of work for purchase of following supplies/services in support of NCI Experimental Therapeutics Project

I. Task Order Request

a. Background

The Pharmaceutical Resources Branch (PRB) of the National Cancer Institute is seeking cost proposal to develop and manufacture a promising anti-cancer agent which was approved under the NCI Experimental Therapeutics Project (next).

The active pharmaceutical ingredient (API) will be produced by one of the synthetic contractors of PRB along with chemical characterization of the agent (IR, NMR, melting point, HPLC analysis, and other tests as required.).

1. Task Order Background

   The project will be issued by RCB, OA, NCI and managed by COR from PRB, Once the project is in place the participants will be the Contracting Official, Contracting Official Representative and the contractor.

b. Scope of Work

This project is intended to support the development and production of a promising cancer agent.

The PRB will provide: 1) the active pharmaceutical ingredient (API) for formulation development studies, the certificate of analysis and a material safety sheet, 2) a HPLC method and 3) stability data on the drug substance as results become available. The contractor is responsible for providing all other consumable supplies and equipment to carry out the tasks noted below

c. Objectives

This task order describes following separate sub-tasks:

1. Development of injectable dosage form – either liquid or lyophilized.
2. Manufacture of a clinical batch based on #1 above following cGMPs suitable for human clinical trials.

d. Project Description and Requirements

The contractor will be responsible for supplying consumable supplies and equipment to carry out the tasks noted below:

1. Studies to develop an injectable dosage form including acquisition of preliminary data to support selection of drug product formulas for intravenous use. Development studies will evaluate the feasibility of both a liquid and lyophilized formulation.

A. Develop a stability indicating HPLC method for the quantification of drug in the presence of excipients. The supplier's HPLC method for the drug substance and

the method used for dose concentration analysis in the toxicology studies will be provided.

B. Determine the solubility of clinical agent in water as a function of pH and cosolvents, if needed under the direction of COR.

C. Develop a freeze drying cycle for the agent in promising formulation using a 10 ml fill volume in a 20 ml 20 mm type I colorless vial. Evaluate for cake appearance, assay, impurities and time to affect complete dissolution after addition of 10 ml 0.9% Sodium Chloride in Water and of 10 ml Distilled Water. A minimum of two pilot freeze drying runs will be required.

D. Once a determination is made of a promising formulation composition, effect of filtration on drug concentration- is determined.

   Prepare about 5 ml of that solution, retain 2 ml, filter 3 ml thorough a 25 mm 0.2 μm PVDF filter. Assay filtered and unfiltered solution in duplicate. The difference content between solutions should be ≤ 2%. If not, evaluate filters with different composition.

E. Stability studies – Aseptic fill solution vs. freeze dried dosage form

   i. The aseptic fill solution, either aqueous or cosolvent formulation should be placed on stability at two different temperatures (for e.g., 25°C/60% relative humidity (RH) and at 40°C/75% RH) at 0, 1, 4 and 12 weeks and evaluate for appearance, assay and impurities.

   ii. Similar studies are to be carried out with lyophilized dosage form except for the attributes to be evaluated include appearance of lyophilized cake, assay, impurities, moisture, reconstitution properties (time to complete dissolution), appearance of reconstituted solution, and pH.

   iii. Assess the stability after reconstitution of the lyophilized drug for injection vials with a) Sodium Chloride Injection USP, and b) Water for Injection, USP at four time points over 3 days, e.g., 0, 6, 24 and 72 hours.

F. Studies to evaluate the antimicrobial properties of the drug product.

   i. The offeror is to carry out the validation test procedure (bacteriostasis/ fungistasis test**)** for sterility by membrane method on the proposed dosage form using the current USP procedure.

ii. A bacterial endotoxin test will also be part of the final product specifications. An enhancement inhibition assessment will be required on the drug product during development.

iii. A filter integrity test will also be required. During development, the offeror is to determine the effect of the clinical agent solution in excipient solution on the

integrity of the 0.2 micron filter using the "bubble point" method and the ability of water for injection flushes to restore the "bubble point" to the preexposure pressure.

2) Manufacture of clinical product

i. Based on the dosage form development studies carried out in part 1, prepare draft manufacturing batch records for preparation of: drug product that include the batch formula card, all the steps used to manufacture the drug product, any in process testing (before and after filtration assays, appearance, pH, etc., fill checks for volume, membrane bubble point following filtration, etc.), all steps in the freeze drying process, vial stoppering, sealing, inspection and labeling. The draft batch records are to be submitted for review and approval by the COR or his designee prior to initiation of manufacture.

ii. For quotation purposes assume batch sizes of 1000-vials of injectable product either liquid or lyophilized product with a freeze drying cycle of 96 hours. Also assume that offeror will be required to repeat the following tests on the drug substance prior to manufacture: appearance, assay, impurities, moisture and identity by infrared spectroscopy. Reference spectra will be provided. The offeror is to provide all consumable supplies (excipients, vials, stoppers, flip off seals, labels, etc.) except the active pharmaceutical ingredient which will be provided by the NCI.

iii. The offeror is to describe their approach to testing of all drug product components (API, excipients, container closure system, labels etc.). The offer is responsible for all in process and final product testing.

Quality control testing and release of drug product

Tests	Specifications
Appearance of lyo product	Report result
Completeness and clarity	TBD following development work of solution
Identity by HPLC	Retention time agrees with reference lot
Uniformity of dosage units	Meets requirements of current USP
Assay (HPLC)	90.0 – 110.0% of label – ave. of three vials
Impurities	report % and RRT of all impurities ≥ LOQ
Particulate Matter (USP 788)	Mmeets requirements
Osmolality	TBD following development work
Moisture (Karl Fisher)	TBD following development work
pH	TBD following development work

Sterility (USP 71)	Meets USP requirements-membrane method
Bacterial endotoxins	TBD depending on maximum human dose.

Following release of the drug products by the offeror, the manufacturing batch records are submitted for review and approval by the COR or designee. The offeror is responsible for storage of the drug products at the labeled temperature until shipping instructions are provided by the COR. Use of these initial batches of drug product requires submission of an IND, receipt of a "study may proceed notice" from the US Food and Drug Administration and IRB approval. Once all approvals are obtained, the COR will provide shipping instruction to the offeror. This process may require at least 3-4 months.

3) Other requested information

i. Offerors are to provide a cost estimate and projected completion date for each of these tasks. One award is anticipated and the offer must be able to carry out all three tasks. The requested tasks are to be carried out under current Good Manufacturing Practices (cGMPs). The offeror's manufacturing facility must be registered with the US Food and Drug Administration. The offerors are to provide a list of the inspections of the facility proposed for this work by FDA and/or other regulatory agencies over the past 5 years. Note if there have been any 483 observations and current status of their resolution.

ii. The offerors are to provide an organizational chart illustrating the reporting relationship of the staff proposed to work on this project.

iii. If certain tasks or tests are not carried out in house, list the organizations that will carry out those functions, the basis for their selection and audit history of those organizations.

e. Conformance and Compliance: Program Policies and Practices

The drug products described in this SOW will be formulated under Good Manufacturing Practice (GMP) guidelines. In addition, all operations described in this SOW will be performed according to the standard operating procedures of the Offeror, and any deviations will be documented.

f. Deliverables

The following table contains a list of deliverables with notation of due dates. All days identified are intended to be normal business days unless otherwise specified. The offeror may suggest an alternative due date for any or all deliverables in their offer. The final schedule will be agreed to by the COR and the offeror based on the offeror's proposed cost and proposed delivery schedule.

i. Deliverable Summary and Due Dates

Deliverable	**Due Date**
• Development of dosage form • Preparation of master production records	6 months from award
Delivery of 1000vials of cGMP drug product	9 Months from award
Dosage from development and batch record documentation (CTD format preferred)	7 Months from award

ii. Deliverable Descriptions and Acceptance Criteria
All drug product shall be developed and manufactured according to the specifications.

iii. Descriptions and Specific Acceptance Criteria
The following deliverables shall be developed in this project. The Offeror's proposed Project Plan should clearly contain all tasks and milestones required to produce these deliverables.

Specific deliverable acceptance criteria are described, below:

1. Deliverable: Development of dosage form.

   Description and Acceptance Criteria: All of the work completed in support of formulation development will be documented in a final report.

2. Deliverable: Dosage from development report and master production records (MPR) which will describe all necessary steps in the manufacturing process as well as the in process procedures required to assure product quality.

   Description and Acceptance Criteria: All of the tasks conducted in support of this project will be documented.

3) Deliverable: Delivery of vials drug product plus executed master production records. All deviations from the master production record will be addressed.

   Description and Acceptance Criteria: All drug product must be manufactured and documented according to cGMP criteria, all applicable institutional standard operating procedures and meet the specifications described elsewhere in this document and. as mutually

agreed upon after completion of development work.

iv. General Acceptance Criteria

- In addition to specific acceptance criteria listed above, general quality measures, as set forth below, will be applied to each deliverable received from the offeror under this task order.
- Accuracy – Deliverables shall be accurate in presentation, technical content, and adherence to accepted elements of style.
- Clarity – Deliverables shall be clear and concise. Any/all diagrams shall be easy to understand and be relevant to the supporting narrative.
- Consistency to Requirements – All deliverables must satisfy the requirements of this task order.
- Timeliness – Deliverables shall be submitted on or before the due date specified in this task order, or submitted in accordance with a later scheduled date determined by the Government.

g. Reporting Requirements

i. Bi-Weekly Team Meetings, as needed

The subcontractor shall manage either face to face or telephone meetings on an every other week, as needed, basis in order to keep the project team appraised of the progress of the project to include any issues or problems. Ad hoc meetings will also be arranged by the offero, as needed. The offeror's responsibilities will include, but are not limited to:

- Securing either a physical location for the meeting, or a suitable call in number and passcode for the relevant participants
- Preparing an agenda of issues for discussion
- Moderation of the meeting

Preparation of the meeting minutes and summarizing any action items resulting from the meeting

ii. Reports and Documentation

a) Dosage form development- After the dosage form development phase is completed, the offer will provide 1) a study report summarizing the findings of the development work including the available data on the stability of the pilot batch; 2) a draft master batch record that reflects the findings and recommendations from the development study and; 3) product specific methods and specifications. The COR or his designee will approve the batch record, methods and specifications prior to production.

b) Manufacture of the dosage forms-Following completion of manufacture, the offer is to provide the executed batch records for drug product to NCI for review and approval.

h. Place of Performance

The majority of the work will be performed at the vendor's facilities. However, the COR may ask that specific tasks, such as testing and demonstrations, be performed at other locations.

i. Period of Performance

Project Initiation Date will commence the date of the award of the Task Order. The list of deliverables includes a notation of due dates based on the start of the contract. All days identified are intended to be normal business days unless otherwise specified. The offer may suggest an alternative due date for any or all deliverables in their offer. The final schedule will be agreed to by the COR and the offeror based on the offero's proposed cost and proposed delivery schedule.

The base period of performance will be 24 months.

j. Government Furnished Data, Materials, or Equipment

The subcontractor will have access to any data generated the project's collaborator(s) relating to this agent that is deemed necessary by the Government to perform the work.

k. Additional Intellectual Property Considerations

None.

II. Technical Proposal Information

Below is a synopsis of the technical information requested from Offerors. Refer to the RFP Document for other requirements and information. Offerors are asked to be direct and concise in presenting information that clearly describes the proposed project. Offerors should realize that the clarity of their proposals is important in communicating the overall project goals to reviewers and that a concise and well formulated proposal will be more easily reviewed and evaluated.

III. General Considerations

Technical proposals shall provide a detailed discussion of the proposed work to enable an in-depth review of the specific technical requirements. Specific attention must be given to addressing the requirements as specified and ordered in the Statement of Objectives.

IV. Specific Considerations

In addition to the general considerations above, the offeror shall address the following areas in their proposals:

a. Executive Summary (1 page limit)

The summary shall contain the most important elements from sections below but should at a minimum clearly specify the following elements:

- Brief identification and qualifications for this solicitation of your organization/team, including any Subcontractors and their roles.
- The purpose and anticipated end result of this proposal.
- Technical and management approach discriminators.
- The summary shall be on separate pages or include a section break before the rest of the proposal.

b. Technical Approach (10 page limit)

1. Understanding
   Provide your understanding of what needs to be done, the scope of the work, the estimated length of time for the work to be finished, the challenges, and how you are going to address those challenges.

2. Approach
   Describe a sound technical approach to the proposed work and critical technology challenges required for accomplishing proposed tasks. Describe any unique aspects of the approach, and why you believe it will be the most efficient and effective way of achieving project objectives. Describe how this approach will meet both project and overall objectives as described in the SOO.

c. Team and Key Personnel (5 page limit)

1. Introduction
   Introduce your organization and/or team here. Give an overview of the capabilities brought to address this effort.

2. Organization and/or Team
   Describe your organization and show chain of command and lines of communication.

   Describe each proposed individual's role and the percentage of their time that is being bid, and a brief description of their qualifications. Fuller experience descriptions may be included in the appendix.

3. Personnel
   All key personnel shall be clearly indicated. Resume summaries for key personnel shall be included in this section, and full resumes in the appendix. The percentage of time each key person is proposed should be clearly indicated here.

d. Experience and Past Performance (5 page limit)

Describe the teams overall experience with development, processes, and technologies similar to those described in this solicitation. Clearly indicate which organization on your team is providing this experience.

Provide a description of at least three projects successfully performed in the past that indicate the ability to perform on this effort. At least one of these projects should have been performed for an organization other than NCI. Clearly indicate who on your team performed, what role was played on each of these projects, and the success criteria that were used to judge the project. Summaries shall be given here and more complete descriptions may be included in the appendix.

E. Project Plan and Work Breakdown Structure (3 page limit)

Describe in summary form the set of tasks that will be performed in order to accomplish project objectives.

Detail the methods for producing deliverables, allocation of staff, and other resources necessary to produce deliverables, and timelines.

Provide a draft project plan in MS Project format as a separate attachment (no page limit). This document should contain tasks that demonstrate how objectives described in the Statement of Objectives will be accomplished. The draft project plan shall show tasks, dependences, and milestones, any milestone reviews as requested in the RPF, as well as any requested Offeror-supplied dates for deliverables.

f. Management Approach (3 page limit)

1. Controls
   Describe your project management approach and what control mechanism you can put in place to track progress and ensure project schedules will be met in according to agreed-upon schedules.

2. Risk Management
   Describe your overall risk mitigation strategy.

   Provide an initial risk table. This table should include a list of project risks, an estimation of the severity of the risk (H,M,L), and a brief risk mitigation approach for that risk.

3. Subcontractor Management
   Describe management controls to be put in place for Subcontractor management if Subcontractors are a part of the proposed team.

4. Financial Tracking
   Describe the mechanism you will use to control budget and cost.

G. Appendix (no page limit)

V. Cost (or Price) Proposal Information Requirements

Proposals which include unrealistic or unreasonable costs may be viewed as a failure to comprehend the complexity of the technical requirements. Proposals shall therefore demonstrate a complete understanding of the requirements and the associated complexities. Failure to adequately demonstrate this understanding and establish realistic costs accordingly may result in a failure to be further considered for award.

Information requested in this attachment is considered to be minimal and further information may be required prior to award of any Task Order.

Specific Considerations:

i. *Section One – Cost (or Price) Proposal*

The cost (or price) proposal shall contain sufficient information to allow NCI to perform an analysis of the proposed cost (or price) of the work proposed. This information shall include the amounts of the basic elements of the proposed cost (or price) including, but not limited to, labor hour rates, travel, materials, Subcontracts.

In preparing your cost (or price) proposal, the following shall be considered:

- Offeror is to prepare their cost (or price) proposal in Microsoft Excel format and submit with Offer.
- Costs shall be broken out by task.
- Offerors shall provide substantive detail regarding the cost (or price) proposed so as to enable reviewers to objectively determine the reasonableness. Failure to provide a level of detail to facilitate this determination may result in the proposal being considered nonresponsive.

ii. Section Two – Cost (or Price) Justification and Documentation

In this section, provide justifications and explanations of the proposed costs. This INCLUDES explanation of the processes by which extended costs were derived and a basis for why the proposed costs should be considered reasonable. The supporting information to be provided includes, but is not limited to:

Labor costs. Provide labor categories and descriptions, if the proposed positions have not been filled or are to be named or hired, provide description of anticipated position and estimated labor category and rate. Demonstration of the reasonableness of any proposed consultant or lower-tier Subcontractor consulting costs, including demonstration that the proposed rates/costs are in keeping with those normally charged for the work to be performed.